REMARKS

Applicants thank the Examiner for his review of the pending application and Applicants' submission transmitted on March 16, 2007. For the reasons below, Applicants respectfully traverse the pending rejections.

Rejection Under 35 U.S.C. §101

The Examiner maintains his rejection of the pending claims under 35 U.S.C. § 101 as lacking utility. The Examiner makes the following arguments in support of his rejection:

1. Gene expression data does not support utility for the claimed antibodies because "Abundant art supports the absence of a necessary relationship between mRNA and protein," and "Protein and DNA Microarray data shows no necessary correlation between mRNA overexpression and protein expression." *Office Action* at 3-9 (emphasis added). The Examiner cites as support, Meric, Gokman-Polar, Pennica, Orntoft, Czupalla, Kwong, Chen, Conrad, Ginestier, Anderson, Washburn, Lee, and Provenzani for support.

2. The Examiner has attacked the sufficiency of the gene expression data, stating that "there is no evidence that the overexpression effect was statistically significant" or "reproducible," that "many genes are irrelevant in gene microarray assays," and that "matched tissue samples were not used for controls." *Office Action* at 10-12. The Examiner cites Li, Ding, and Sawiris for support.

3. Finally, the Examiner argues that "[s]pecific data shows that Pro539 is NOT overexpressed in lung tumors." *Office Action* at 13-15.

The Board of Patent Appeals and Interferences has Affirmed Applicants' assertion that overexpression of mRNA in tumors is sufficient to establish a specific and substantial utility for the encoded polypeptide

In a non-precedential opinion involving many of the same inventors of the instant application, *Ex parte Goddard*, Appeal No. 2006-1469, the Board of Patent Appeals and Interferences (Board of Appeals) held that microarray data demonstrating overexpression of a gene in tumors compared to non-cancerous controls is "sufficient to establish a specific and substantial utility for the polypeptide," even though there was no data regarding expression of the

claimed polypeptide. *Ex parte Goddard* at 9 (opinion attached as Exhibit 1 for Examiner's convenience). In that appeal, the Board of Appeals reversed the examiner's §101 utility rejection, rejecting many of the arguments made by the Examiner in the instant application. Of particular note, the Board of Appeals stated:

> The microarray data demonstrates that mRNA for the PRO1866 polypeptide (SEQ ID NO: 14) is overexpressed in colon tumor, prostate tumor, and lung tumor, as compared to universal normal control. Thus, the polypeptide of SEQ ID NO:14 has a significant and presently available benefit to the public as a tumor marker.
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> We have considered the Examiner's assertions that microarray analysis measures mRNA levels, and not overexpression of the polypeptide of SEQ ID NO:14 itself. As demonstrated by the Polakis and Smith Declarations, however, there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that.
>
> Finally, the use of the PRO1866 polypeptide as a cancer marker is sufficient to demonstrate utility, and there is no requirement that a causative link between the polypeptide (or nucleic acid) of the present invention and colon, lung or prostate tumors be demonstrated. *Id.* at 9-10 (emphasis added).

Given the Board of Appeal's opinion in *Ex parte Goddard*, Applicants respectfully request that the Examiner reconsider his utility rejection, as Applicants have established that PRO539 mRNA is overexpressed in a significant number of lung tumors tested by Applicants, including a majority of squamous cell lung tumors. *See Smith Declaration* at ¶7. In addition, nearly all of the Examiner's arguments in support of his utility rejection have been addressed and rejected by the Board of Appeals.

The Board of Appeals has rejected the Examiner's argument that there is no relationship between mRNA and protein expression

The Examiner has argued that the polypeptide related to the claimed antibody lacks utility because there is "no necessary correlation between mRNA overexpression and protein expression." *Office Action* at 5 (emphasis added). In the Examiner's Answer brief in *Ex parte Goddard*, the examiner made similar arguments:

> [T]he microarray analysis merely measures the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO: 14. There is no evidence regarding whether the level of PRO1866 polypeptide of SEQ ID NO: 14 or, even more broadly, its variants significantly increased in colon, lung or

prostate tumor samples in comparison with the normal control. *Examiner's Answer Brief* at 16 (hereinafter "Answer Brief," attached as Exhibit 2 for Examiner's convenience) (emphasis added).

Appellant's reasoning is flawed logically and does not account for a gap between a gene expression level and a protein level. The molecule detected by the microarray was one specific mRNA that is complementary to the nucleic acid of SEQ ID NO: 13 and encodes the polypeptide of SEQ ID NO: 14, not the polypeptide of SEQ ID NO: 14, not the variants of the polypeptide of SEQ ID NO: 14. There is no correlative link established between the level of gene expression and the level of the protein in general (see below for details). *Id.* at 18 (emphasis added).

Clearly, Appellant's argument that a positive correlation exists between mRNA and protein is not true. ...Haynes et al. conclude "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (bottom of left column of page 1870). Accordingly, the limited disclosure in the instant case does not meet the legal standard for a specific and substantial utility required under 35 U.S.C.§ 101. *Id.* at 24 (emphasis added).

There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoding polypeptide. In fact, the art teaches the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (Haynes et al., Electrophoresis, 19:1862-1871, 1998; see, left column of page 1863; Figure 1). *Id.* at 30 (emphasis added).

In response to the examiner's arguments in *Ex parte Goddard*, the Board of Appeals **rejected** the argument that mRNA expression levels do not reflect protein expression levels:

We have considered the Examiner's assertions that microarray analysis measures mRNA levels, and not overexpression of the polypeptide of SEQ ID NO:14 itself. As demonstrated by the Polakis and Smith Declarations, however, there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that. *Ex parte Goddard* at 9 (emphasis added).

The same facts are present in the instant case. Applicants have made of record a declaration of Dr. Polakis, where he makes the same statements relied on by the Board of Appeals. Similarly, in the declaration by the same Dr. Smith, previously made of record in the instant case, she states:

> It is well-established in the art that overexpression of the mRNA for a gene is likely to lead to overexpression of the corresponding protein. ... Given the known correlation between overexpression of a gene and the corresponding overexpression of the encoded protein, it is very likely that a similar number of lung tumors will overexpress the PRO539 protein, while very few normal lung tissue samples likely will. *Smith Declaration* at ¶¶6-7 (emphasis added).

In addition to the declarations by Drs. Polakis and Smith, Applicants have made of record the declaration of J. Christopher Grimaldi, who states: "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed, as evidenced by an increased production of mRNA, the gene product or polypeptide will also be over-expressed." *Grimaldi Declaration* at ¶5. Likewise, the declaration of Dr. Scott, an independent expert states: "[G]enerally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. ...[I]t has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue." *Scott Declaration* at ¶10. These statements are supported by the numerous references made of record by Applicants (Exhibits 1, 2, 4, 5, several of the references submitted as Exhibit 7, and Exhibits 10-19, submitted with Applicants' response mailed April 26, 2006.) In sum, Applicants have made of record the opinions of the same experts relied on by the Board of Appeals in *Ex parte Goddard*, as well as two additional experts and numerous supporting references.

Thus, as in *Ex parte Goddard*, Applicants have established that "there is a strong correlation between mRNA levels and protein expression." *Ex parte Goddard* at 9. And, as in *Ex parte Goddard*, "the Examiner has not presented any evidence specific to the PRO[] **polypeptide** to refute that." *Id.* (emphasis added). Given these facts, Applicants respectfully request that the Examiner reconsider his utility rejection, as the Board of Appeals has rejected his position that evidence of polypeptide overexpression is required – overexpression of the mRNA is sufficient to establish the utility of the encoded protein.

The Board of Appeals has rejected the Examiner's argument that the overexpression data needs to be statistically significant and relative to tissue matched control, or is otherwise "irrelevant"

The Examiner in the instant case has argued that the data showing amplification and overexpression of PRO539 nucleic acids are insufficient because there is no evidence that they

are statistically significant, reproducible, not the result of nonspecific effects or a single tumor sample, or simply biologically irrelevant. *Office Action* at 10-12. In addition, the Examiner argues that tissue matched controls are required. *Id.* at 12. In the Examiner's Answer Brief in *Ex parte Goddard*, the examiner made these same arguments regarding the sufficiency of Applicants' data:

> There is no statistical analysis or validation analysis of the expression data. Numerous questions remain to be answered: such as how many tumor samples and normal control samples were used in the study? How were the normal control samples pooled? What types of colon, lung or prostate tumor samples were utilized in the assay (there are different types of lung tumors, for example)? What were the actual level or relative degree of expression of the protein or the nucleic acid encoding the polypeptide in the universal control versus the tumor samples? How to distinguish a truly positive hybridization signal from a false one? How many fold difference in the expression level between a tumor sample and a normal control was considered as being significant? Without such critical information, how would one of skill in the art be able to quantitatively compare the level of PRO1866 expression in a tumor sample to a normal control sample and to detect a relative difference in the level of PRO1866 expression between the tumor and normal samples? *Answer Brief* at 19 (emphasis added).
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> [S]tatistical analysis and validation analysis are needed to establish a marker for diagnosis of a certain type of tumor, for example, lung adenocarcinomas. A sufficient sample size (i.e., number of tumor samples and healthy control samples) is required for assessment of the difference in the expression level of a gene or protein at a given significance level (e.g., $P<O.01$). Without such an analysis, one of skill in the art would not be able to judge whether a nucleic acid or a protein can be practically used as a diagnostic marker for a specific type of tumor. *Id.* at 22 (emphasis added).
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> Hu et al. clearly states: "it is not uncommon to see expression changes in microarray experiment as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful" (bottom of right column of page 411). Hu et al. further states: "in any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study" (1st paragraph of left column of page 405).
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> Accordingly, in view of the limited disclosure in the instant case--lack of disclosure of the "cut-off ratio" that was used to determine whether a hybridization signal was significant, lack of the statistical analysis, lack of the validation of universal normal control, and lack of establishment of a correlative link between gene expression and protein level or a causal link between gene expression and colon, lung or prostate tumours, the teachings of Hu et al. support the Examiner's position that further research is needed to reasonably identify or

> confirm a specific and substantial utility for the instantly claimed polypeptide of SEQ ID NO: 14 and its variants. *Id.* at 27 (emphasis added).
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> Furthermore, the specification provides no information regarding the specific degrees of the increase in mRNA level or protein levels of PRO1866 in tumor tissues relative to corresponding normal tissues. There is no statistical analysis of the expression data. For example, there is no disclosure of the number of tumor samples and control samples that were analyzed, which is clearly required for the establishment of a reliable diagnostic marker for colon, lung or prostate tumors. *Id.* at 30-31 (emphasis added).

From the above quotes, it is apparent that the Board of Appeals was presented with the same arguments in *Ex parte Goddard* that the Examiner is making in the instant case regarding the sufficiency of the nucleic acid expression data. The Board of Appeals **rejected** the examiner's assertion that the data were irrelevant or insufficient in any way, stating that the microarray data were "sufficient to establish a specific and substantial utility" for the claimed polypeptides. *Ex parte Goddard* at 9. Given the Board of Appeal's rejection of the examiner's attempts to heighten the utility standard in *Ex parte Goddard*, Applicants respectfully request that the Examiner withdraw his utility rejection of the instant claims based on the same flawed reasons.

The Examiner also argues that "the art supports the conclusion that many genes are irrelevant in gene microarray assays." *Office Action* at 10. Relying on Li, Ding, and Sawiris, the Examiner concludes that "the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all. The current gene, Pro539, is such a gene." *Id.* at 11. The Examiner concludes given "the absence of any direct association with Pro539 and lung tumors, this gene represents noise. ... Therefore, genes such as Pro539, lack substantial utility as useful on gene expression arrays." *Id.*

Applicants have previously addressed these arguments and cited references, and will not repeat their arguments here. However, Applicants note that the Board of Appeals rejected a similar argument by the examiner in *Ex parte Goddard*, who argued that "Hu et al. further states: 'in any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study.'" *Answer Brief* at

27 (emphasis added). The additional references cited by the Examiner in the instant case do not provide any additional reason for the Board of Appeals to reach a different conclusion here.

Applicants' evidence establishes that the PRO539 mRNA is overexpressed in a significant portion of lung tumors tested, and a majority of squamous cell lung tumors tested

The only one of the three arguments made by the Examiner in the instant case that was not presented to the Board of Appeals and subsequently rejected in *Ex parte Goddard*, is the Examiner's argument that "[s]pecific data shows that Pro539 is NOT overexpressed in lung tumors." *Office Action* at 12-15. To support this statement, the Examiner cites two datasets for Kif7 gene expression from the NCBI website. The first is from a study titled "Lung neuroendocrine tumor classification," and the second is from a study titled "Colorectal carcinoma subtype with microsatellite instability." The Examiner characterizes the first study as finding "no correlation whatsoever between expression and cancer," and the second study as appearing to show "no relationship with cancer."

Applicants note that in the second study, all of the samples tested were tumor samples. Because there are no normal controls of any kind, it is impossible to say whether Kif7 is overexpressed in colorectal tumors relative to normal tissue. Therefore, these data provide no support for the Examiner's position.

While the first study appears to show overexpression of Kif7 in only a few (four) tumor samples relative to controls, none of the control samples show overexpression of Kif7. This is similar to Applicants' data previously submitted with the declaration of Dr. Smith. Dr. Smith states in her declaration that:

> [T]he gene encoding PRO539 (DNA47465) is significantly overexpressed in eight of the twenty-six lung tumor samples tested compared to the normal lung tissue controls. That is the equivalent of nearly one in every three samples (31%). In addition, four out of five squamous cell lung carcinomas (80%) are significantly overexpressed (shown in bold). In contrast, only one of the seven individual normal lung tissue samples shows significant overexpression of the PRO539 gene (14%). *Smith Declaration* at ¶5.

Given the overexpression of PRO539 in a significant portion of lung tumors tested, including a majority of squamous cell tumors, and only a single normal tissue showing

overexpression, Dr. Smith concludes that PRO539 nucleic acids, polypeptides and antibodies are useful as diagnostic tools:

> Given the known correlation between overexpression of a gene and the corresponding overexpression of the encoded protein, it is very likely that a similar number of lung tumors will overexpress the PRO539 protein, while very few normal lung tissue samples likely will. Together with the data reported in Example 16 that the gene encoding PRO539 is amplified in some lung tumors, including squamous cell lung carcinoma, the results reported in Exhibit B indicate that the PRO539 gene and protein, as well as antibodies to the encoded protein, can be used to differentiate some cancerous lung tissue, particularly squamous cell carcinoma, from normal lung tissue. Because not all lung tumors show overexpression of PRO539, it cannot be used to exclude a sample being tested as non-cancerous. However, the PRO539 gene, protein, and corresponding antibodies are useful as a diagnostic tool for lung cancer, particularly squamous cell carcinoma, since a very high percentage of squamous cell lung carcinomas overexpress the gene and most likely the encoded protein, while very few normal lung samples do. *Smith Declaration* at ¶7 (emphasis added).

Nothing in the results of the "Lung neuroendocrine tumor classification" study are contrary to Dr. Smith's opinion or accompanying data. Therefore, even if the Examiner's characterization of the Kif7 lung tumor study is correct, it is not contrary to Applicants' own data and does not provide a basis to reject the conclusions of Dr. Smith. Because this argument does not support the Examiner's utility rejection, and the Examiner's other arguments have been presented to the Board of Appeals and rejected, Applicants respectfully request that the Examiner withdraw his utility rejection of the pending claims.

The Examiner's cited references are Not Relevant to determining whether a change in mRNA level for a particular gene leads to a corresponding change in the level of the encoded protein

As noted above, the Board of Appeals has rejected the Examiner's position that overexpression of mRNA in tumors is not sufficient to provide utility for the claimed polypeptide. However, in the interest of thoroughness, Applicants respond below to the Examiner's argument that "[n]ine out of ten recent microarray papers show discordant protein and mRNA expression data." *Office Action* at 6-9.

As an initial matter, Applicants reiterate that Applicants' asserted utility does not require that all changes in protein levels result from changes in mRNA level. Applicants' assert that, as a general rule, gene amplification leads to overexpression of the mRNA and encoded protein.

The fact that protein levels can change in the absence of gene amplification or a change in mRNA is not relevant to Applicants' asserted utility – Applicants are not trying to determine or predict mRNA levels by examining changes in protein level.

The Examiner has yet to explain his continued reliance on data purportedly showing protein changes in the absence of mRNA changes. His only response is that "this is directly relevant because it goes to the question of whether mRNA level data is representative of protein level data." *Office Action* at 31. This is not an explanation as to how this data is in any way relevant. The question is not whether mRNA level data is representative of protein level data, but whether overexpression of mRNA leads to overexpression of a protein – if the mRNA level remains unchanged, the data offers no insight into the issue at hand. There could be an absolute, perfect and necessary correlation between increased mRNA expression leading to increased protein expression, but still be cases where protein expression changes in the absence of a change in mRNA expression. This is because a change in mRNA expression can be a sufficient cause (i.e., it always causes), but not necessary cause (i.e., other causes exist), of changes in protein expression. The Examiner's statement requires further explanation as it is contrary to basic principles of cause and effect.

a. Czupalla, Kwong, Chen, Conrad, Ginestier, Anderson, and Washburn

Applicants have previously addressed the Czupalla, Kwong, Chen, Conrad, Ginestier, Anderson, and Washburn references, and will not repeat their arguments here.

It is worth noting that Haynes, *et al.* (Electrophoresis, 19(11):1862-71 (1998)) conducted a study similar to those in Kwong, parts of Chen, Conrad and Anderson, i.e., a study that depends on a global mRNA:protein ratio across different genes to find a correlation between mRNA and protein levels. Applicants have explained at length why such studies are not relevant. The examiner in *Ex parte Goddard* relied on the Haynes reference to support the argument that mRNA levels cannot be used to predict protein levels:

> Clearly, Appellant's argument that a positive correlation exists between mRNA and protein is not true. ...Haynes et al. conclude "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (bottom of left column of page 1870). Accordingly, the limited disclosure in the instant case does not meet the legal standard for a specific and substantial utility required under 35 U.S.C.§ 101. *Answer Brief.* at 24 (emphasis added).

> There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoding polypeptide. In fact, the art teaches the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (Haynes et al., Electrophoresis, 19:1862-1871, 1998; see, left column of page 1863; Figure 1). *Id.* at 30 (emphasis added).

The Board of Appeals did not find the examiner's arguments based on Haynes *et al.* persuasive, as the Board of Appeals reversed the examiner's utility rejection. Applicants submit that for the same reasons, the Board of Appeals will find the Kwong, Chen, Conrad and Anderson references unpersuasive.

b. Lee et al.

The first new reference cited by the Examiner is Lee, which the Examiner quotes as stating: "Consistent with observation in other organisms, we observed no clear relationship between mRNA amplification and protein amplification factors for Escherichia coli." *Office Action* at 8-9.

Like the experiment by Washburn, the experiments of Lee are more relevant to Applicants' assertions than the experiments by Haynes, Kwong, Chen, Conrad and Anderson discussed above. This is because Lee plots the ratio of mRNA in two conditions against the ration of protein expression in the two conditions – Lee is attempting to examine changes in mRNA expression. However, as Figures 3 and 4 indicate, the conditions examined by Lee did not result in significant changes in mRNA. Instead, the vast majority of the data points have between 0.5 and 2 mRNA amplification factor, indicating that they had less than a two-fold change in mRNA level. Because the level of mRNA is not changing, there is no way of observing an affect on the level of protein expression. While Figure 3B does have a few data points that show greater than 2-fold changes in mRNA level, most of which do not show a corresponding change in protein level, this is hardly a "global comparison" as suggested by the Examiner. It is at best, a single study in which the authors demonstrate that under a minor environmental perturbation of *E. coli* by the addition of IPTG, approximately 17 genes showed a change in gene expression without an equivalent change in protein expression. It should not be

given any special weight in considering Applicants' assertions, and must be considered along with the four expert declarations and dozens of references submitted by Applicants.

c. Provenzani et al.

The second new reference cited by the Examiner is Provenzani, which the Examiner characterizes as a comparison of total mRNAs and polysomal mRNA, "which are the mRNAs which will undergo translation into protein. *Office Action* at 9. The Examiner quotes Provenzani as stating that "our analysis shows that 80% of the genes undergoing a gene expression change in the transition between SW480 and SW620 cells do it by varying their degree of polysomal loading, implying a dramatic subversion in the signaling control of translation and/or in the translational machinery itself." *Id.* (emphasis added). The Examiner concludes that Provenzani "supports the conclusion that up to 80% of genes will not show differential expression based upon mRNA level, but rather based on polysomal loading, so that mRNA level will not provide significant information regarding the utility, or lack thereof, for the protein." *Id.*

Applicants submit that the Examiner is again confusing cause and effect, and the difference between attempting to predict changes in mRNA levels from changes in protein levels, rather than trying to predict changes in protein levels based on changes in mRNA levels. Even if Provenzani is correct, and polysomal mRNA loading is an accurate indirect measure of protein levels, all that can be concluded from their statement is that 80% of proteins with changed expression levels do not rely on changes in total mRNA level. However, this does not mean that changes in total mRNA levels to not result in corresponding changes in protein levels – the issue at hand. If, as Applicants assert, there is generally a corresponding change in protein level when mRNA levels are changed, then one can predict changes in protein level from changes in mRNA level. The statement that 80% of genes studied by Provenzani do not rely on changes in total mRNA level, even if true, is not contrary to Applicants' assertions – changes in protein level in the absence of changes in mRNA level are not contrary to Applicants' assertions.

Conclusion – the Examiner's arguments are not sufficient to provide a basis for one of skill in the art to doubt Applicants' asserted utility

Applicants have shown that nearly all of the references relied on by the Examiner are either irrelevant, not contrary to Applicants' assertions, or actually support Applicants' position,

not the Examiner's. Taken together, the Examiner's arguments are not sufficient to satisfy the burden to "provide[] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Instead, considering all of the evidence of record, including four expert declarations, and dozens of supporting references, an unbiased observer would conclude that it is more likely than not that overexpression of PRO539 mRNA leads to overexpression of PRO539 protein, and therefore the claimed antibodies have a specific and substantial utility. This is the conclusion that the Board of Patent Appeals and Interferences reached in a similar case: "We find that the microarray data [showing overexpression in certain tumors] is sufficient to establish a specific and substantial utility for the polypeptide." *Ex parte Goddard* at 9 (emphasis added). In light of the evidence of record and the proper legal standards established by the courts and adopted by the Board of Appeals in *Ex parte Goddard*, Applicants respectfully request that the Examiner withdraw the utility rejection of the pending claims.

Rejection under 35 U.S.C. §112 – Enablement

The Examiner also rejects Claims 22-26 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner cites *In re Wands* and the factors set forth therein to determine the scope of enablement. The Examiner's arguments are largely the same as those for the utility rejection. *Office Action* at 16-31. In particular, the Examiner argues under the "unpredictability of the art and state of the art" heading that there is no "necessary" between mRNA and protein levels, citing the same references relied on for the utility rejection. *Office Action* at 18-30.

For the reasons of record, Applicants submit that the claimed antibodies are enabled, as one of skill in the art would know how to make and use them. Applicants submit that the evidence, declarations, references, and arguments discussed above make clear that Applicants have established that it is more likely than not that one of skill in the art would be convinced that the PRO539 protein is overexpressed in certain cancers, and therefore antibodies to PRO539 have utility as a diagnostic tool. In addition, in *Ex parte Goddard*, the Board of Appeals has held

that overexpression of the nucleic acid is sufficient to establish utility for the encoded polypeptide. To the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

As to the Examiner's recitation of the *In re Wands* factors, Applicants note that the question of enablement regarding antibodies is the very issue that was addressed in *In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988). In *Wands*, the CAFC held that the disclosure was sufficient to enable one of skill in the art to make monoclonal antibodies to a disclosed antigen without undue experimentation. *Id.* at 740. If the disclosure was sufficient at the time of filing of the *Wands* application in 1980, it cannot be that the art of making antibodies has become less predictable in the ensuing 25 years, and now requires undue experimentation.

In addition, Applicants submit that the specification discloses how to make and use the claimed antibodies. For example, Example 27 on page 127 of the specification specifically describes the preparation of antibodies that bind PRO polypeptides. *Specification* at 90, line 20 through 97, line 4, and 127, line 13, through 128, line 1. The specification also discloses that the claimed antibodies can be used in diagnostic assays to detect the expression of PRO539 in specific types of tissue. *Specification* at 98, lines 5-29.

Therefore, given the teaching in the specification on how to make and use the claimed antibodies to detect expression of PRO539 in specific tissues, one of skill in the art would be enabled to practice the claimed invention without undue experimentation. Thus, at least one use of antibodies to the PRO539 polypeptide is adequately enabled, which is all that is required – "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." *M.P.E.P.* § 2164.01(c). In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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